

fMRI Localization of Spinal Cord Processing Underlying Female Sexual Arousal

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Using functional magnetic resonance imaging, the authors aimed to determine the roles of the human spinal cord in mediating sexual responses in women. Functional magnetic resonance imaging of the entire lower thoracic, lumbar, and sacral spinal cord was performed using a sexual stimulation paradigm designed to elicit psychological and physical components of sexual arousal. Responses were measured in 9 healthy adult women during 3 consecutive conditions: (a) erotic audiovisual, (b) manual clitoral, and (c) audiovisual plus manual stimulation. Functional magnetic resonance imaging results in healthy subjects demonstrate that this method is sensitive for mapping sexual function in the spinal cord, and identify several key regions involved in human sexual response, including the intermediolateral cell column, the dorsal commissural nucleus, and the sacral parasympathetic nucleus. Using spinal functional magnetic resonance imaging, this study identified many of the spinal cord regions involved in female sexual responses. Results from audiovisual and manual clitoral stimulation correspond with previous data regarding lumbar and sacral neurologic changes during sexual arousal. This study provides the first characterization of neural activity in the human spinal cord underlying healthy female sexual responses and sets a foundation for future studies aimed at mapping changes that result from sexual dysfunction, spinal cord trauma or disease.

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INTRODUCTION

Until the development of functional magnetic resonance imaging (fMRI) and its specific adaptation for use in the spinal cord (spinal fMRI), noninvasive in vivo studies of human spinal cord activity were not possible (Leitch, Figley, & Stroman, 2010; Stroman, 2005; Stroman et al., 2014). Therefore, to obtain information about spinal cord responses, researchers relied on animal experiments (Cai, Alexander, & Marson, 2008; Marson & McKenna, 1990; Truitt & Coolen, 2002) or clinical studies of the effects of trauma (Courtois, Goulet, Charvier, & Leriche, 1999; Sipski, Alexander, & Rosen, 1995, 2001). While these studies have helped shape our current understanding about the neural underpinnings of sexual responses, our knowledge of human spinal cord function during female sexual stimulation is based on very little direct evidence from neurologically intact humans (Giuliano, Rampin, & Allard, 2002; McKenna, 2002).

On the basis of animal models and patients with specific neurologic injuries, we know that the human sexual response is mediated by integrated functions with psychogenic, reflexogenic, and somatic components (Giuliano et al., 2002; Levin & Riley, 2007; Neuhuber, 1982; Schroder, 1980). In general, psychogenic sexual responses in humans are controlled by the thoracolumbar segments, T11 to L2, whereas reflexogenic aspects are mediated by the sacral segments, S2 to S5. The psychogenic component is mediated by sympathetic preganglionic neurons in the dorsal commissural nucleus and the intermediolateral cell column (Giuliano et al., 2002). In contrast, the reflexogenic component is thought to be controlled by preganglionic neurons in the sacral parasympathetic nucleus and by pelvic and pudendal nerve afferents from the clitoris, which terminate in the sacral parasympathetic nucleus, dorsal gray commissure, and the dorsal horn (Marson & Murphy, 2006; McKenna, 2000, 2002; McKenna & Marson, 1997; McKenna & Nadelhaft, 1986). The somatic component of the sexual response is found in Onuf's nucleus, which controls muscle and sphincter contraction during penile erection and ejaculation in men (Schroder, 1981; Xu et al., 2007),but is poorly understood in women's sexual function.

We recently published a spinal cord functional MRI study in able-bodied men (Kozyrev, Figley, et al., 2012), which confirmed advanced spinal fMRI acquisition and analysis methods can be used noninvasively to elucidate neural correlates of human spinal sexual responses in men. Therefore, the purpose of the present study was to use similar methods to characterize spinal cord activity in response to sexual stimulation in neurologically intact women. We aimed to determine which regions of the thoracolumbar and sacral human spinal cord play a role in mediating sexual responses in healthy women, allowing us to validate, refute, or refine, long-held assumptions from previous animal and clinical studies.

METHOD

Participants

Spinal cord responses in the lower thoracic, lumbar, and sacral areas were measured in nine healthy female volunteers (mean age = 20.7 ± 2.3 years). All underwent screening before testing to ensure that they found erotica sexually arousing and were comfortable with genital stimulation. The Queen's University Health Science Research Ethics Board approved the study and all subjects provided written informed consent before participating.

Arousal Paradigms

Similar to our previous study of male sexual responses (Kozyrev, Figley, et al., 2012), this study consisted of three conditions designed to elicit neural responses from psychological and/or physical sexual activity. On the basis of previous studies (Sipski, Alexander, & Rosen, 1997; Sipski et al., 2001), conditions included audiovisual stimulation (AV) to elicit psychological arousal/psychogenic responses; manual stimulation (MAN) to elicit physiological arousal/reflexogenic responses; and combined audiovisual plus manual stimulation (COM) to simultaneously elicit psychogenic and reflexogenic responses.

During the AV (i.e., psychogenic) condition, participants viewed erotic films in two 5-min blocks separated by a 3-min baseline condition (blank screen) and preceded and followed by 1.5-min baseline conditions. During the MAN (i.e., reflexogenic) condition, participants performed self-stimulation of the clitoris using a small, custom-made, MRI-compatible vibrator without erotic visual stimuli (only written instructions that indicated to "stimulate" or "rest"). In this way, MAN was performed in two 1.5-min blocks of stimulation that were separated by a 1.5-min rest condition, and preceded and followed by 1.5-min rest conditions. The final stimulation paradigm (COM) involved a combination of audiovisual and manual genital self-stimulation, in which, after an initial 1.5-min baseline condition, participants viewed erotic films and self-stimulated with the vibrator for 20 min or until orgasm (which was verbally reported by subjects via the in-scanner intercom).

To impose consistency across subjects, the same erotic films were shown, in the same order, to all study participants during the first and third (AV and COM) study conditions. The erotic films were chosen because they received high subjective rankings (greater than 8 out of 10) by a group of independent viewers similar to Kozyrev, Figley, and colleagues (2012). Because our goal was to have subjects achieve maximum arousal, but not orgasm, during each of the first two stimulation paradigms, the second part of the study (MAN) was shortened compared with the audiovisual condition.

Subjective Measures of Sexual Arousal

Before the study, subjects were informed that they would be asked throughout the study about their levels of mental and physical sexual arousal. For these purposes, mental sexual arousal (MSA) was defined as feelings and mental imagery associated with the desire and motivation to engage in sexual behaviors, while physical sexual arousal (PSA) was defined as physical changes such as vaginal lubrication. Subjects were asked to rate these measures on a scale ranging from 1 (*very little or no sexual arousal*) to 10 (*greatest possible sexual arousal*) at the beginning of the experiment, as well as at end of each of the three stimulus conditions. Subjects were also asked to indicate verbally if and when an orgasm occurred.

fMRI Data Acquisition and Analysis

Data acquisition and analysis procedures used in the present study were replicated from our previous study on male subjects (Kozyrev, Figley, et al., 2012). Imaging was briefly performed with a 3T whole-body MRI system. Participants were positioned on a phased-array spine coil, aligned and centered at the T12 vertebral level. An optical sensor was attached to the second digit

of the nonstimulating hand to record the peripheral pulse throughout the study. Initial three-plane localizer images were acquired, and were used for subsequent slice positioning. An optimized spinal fMRI sequence (Stroman, Kornelsen, & Lawrence, 2005) was then used to measure task related signal changes based on a combination of BOLD and SEEP contrast (for review, see Figley, Leitch, & Stroman, 2010). This was achieved by acquiring predominantly proton-density-weighted images from nine contiguous, 2-mm-thick sagittal slices—spanning the thoracolumbar (T7–L2) and lumbo-sacral (L3–S4) spinal cord regions—using a half-Fourier single-shot fast spin-echo (HASTE) MRI sequence, with the following parameters: TE = 38 msec; TR = 9 sec (i.e., 1 sec per slice); FOV = 280 mm × 140 mm, spatial resolution = 1.5 mm × 1.5 mm × 2 mm. Spatial saturation pulses were applied to suppress signals originating from anterior to the spine and outside of the imaging field-of-view, and flow-compensation gradients were applied in the head-foot direction to minimize potential artifacts from cerebrospinal fluid flow. With these acquisition parameters, each 16-min paradigm for the AV condition spanned 107 fMRI volumes, the 7.5-min paradigm for MAN condition spanned 50 volumes, and the COM condition spanned up to 147 volumes or until the subject achieved orgasm.

Spinal fMRI data processing and statistical analyses were carried out using custom-made software written in MATLAB. Each participant's spinal fMRI data were subjected to a first-level analysis, where regions of spinal cord activity related to each task were identified using a mass univariate approach. The time-course of each voxel was fit with a general linear model to identify regions that were temporally correlated with each of the task paradigms. The components of the general linear model consisted of the task time-courses, a constant function, a linear ramp (to account for scanner drift over the course of each scan), and three slice-specific physiological motion regressors, as previously described (Figley & Stroman, 2009). Following the first-level analyses, each participant's data were spatially normalized to a standard spinal cord template (Stroman, Figley, & Cahill, 2008) to enable second-level (i.e., across-subject) random effects analyses for each task condition. Thus, activity maps were created to identify regions of consistent activity during AV, MAN, and COM conditions with user-defined statistical thresholds (T > 2.5 or T < -2.5, p < .008).

Given the nature of spinal fMRI (and this study in particular), several precautions were taken in an attempt to reduce and eliminate possible motion artifacts. First, subjects were given detailed information about the consequences of bulk motion in MRI data, and were instructed to "remain as still as possible throughout the experiment." Second, masking tape was placed across each subject's torso and abdomen during the initial setup to increase awareness of bulk motion. Third, spatial saturation pulses and flow-compensation gradients were used to minimize signals originating from beyond the spinal cord, and due to cerebrospinal fluid flow, respectively. Fourth, although spinal cord motion is attenuated in the lower-thoracic, lumbar, and sacral regions compared with the cervical and upper-thoracic levels (Figley & Stroman, 2007; Figley, Yau, & Stroman, 2008), time-series spinal fMRI data were analyzed using a motion-compensating general linear model analysis to account for cardiac-related physiologic noise (Figley & Stroman, 2009). Because of the potential for involuntary muscle contractions and bulk motion, images acquired at the time of subject-reported orgasm were excluded from the fMRI analysis. Each volume of the time-series data was also compared with the first volume of the series, and if the spatial correlation dropped below a threshold of R = 0.85, the volume was not used in the general linear model analysis. This accommodated brief bulk body displacements, and use of subsequent volumes in the analysis, if the person then returned to their original position.

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FIGURE 1 Regions of the spinal cord that control sexual responses in nine healthy able-bodied women. (a) Histological reference of spinal cord regions. (b) Combined spinal fMRI datasets from nine healthy women for all three experimental conditions: audio-visual (AV) stimulation, clitoris self-stimulation (SS), Genital Stimulation, and combined audiovisual and clitoris self-stimulation (AV & SS). For each dataset, functional activity is overlaid on high resolution anatomical images of the spinal cord (T/L = thoracolumbar, S = sacral). The color bar on the right quantifies positive (red) and negative (blue) signal intensity changes corresponding to increased and decreased activity respectively.

RESULTS

To ensure that subjects were sexually aroused during the procedures, each participant verbally indicated their level of MSA and PSA at the end of each study epoch (Table 1). MSA was significantly higher during the CAM condition compared with either audiovisual or MAN (p = .003). In contrast, PSA significantly increased during each successive phase of the study (p < .001). Results reveal that MSA and PSA were closely linked during the AV and MAN study phases, but there was not a significant difference between MSA and PSA at the end of the CAM period.

In the present study, fMRI results are thought to demonstrate the anatomical locations of responding spinal cord regions and the relative changes in (presynaptic) neural input to these regions (Figley et al., 2010; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Consistent with the rodent literature, the AV condition elicited spinal fMRI responses throughout the thoracolumbar spinal cords of our subjects, particularly in regions of the intermediolateral cell column and the dorsal commissural nucleus (Figure 1). During AV stimulation, spinal fMRI responses were also observed in the left sacral parasympathetic nucleus and dorsal horn of the sacral spinal cord. Compared with baseline, the MAN condition produced decreased fMRI signal in the right ventral horn and increased fMRI responses in a large area to the right of the central canal in the lumbar spinal cord, in segments L1–L4. During the CAM condition, negative thoracolumbar signal changes were observed in the right intermediolateral cell column, right ventral horn and right dorsal horn, and positive sacral cord responses were observed in the right sacral parasympathetic nucleus. Similarly to the MAN condition, increased signal changes were observed in a large region to the right of the central canal in the right of the central canal in the right socral parasympathetic nucleus. Downloaded by [JHU Libraries] at 16:37 15 January 2016

		Arc	usal Levels Durin	IABLE g Various	1 Experime	ental Cond	titons
					Audiov	isual and	
	Audiovi	sual stimulation	Manual stimu	lation	manual	stimulation	
Type of arousal	Μ	SD	М	SD	Μ	SD	Significance
Mental arousal	5.11	1.90	5.78	0.83	7.67	1.94	Mental arousal during audiovisual plus manual stimulation was significantly higher than mental arousal during audiovisual or manual stimulation alone.
Physical arousal	4.89	1.82	6.89	1.54	8.22	1.86	Physical arousal during audiovisual plus manual stimulation was significantly greater than during manual stimulation alone and manual stimulation alone was significantly greater than during audiovisual stimulation alone.
Statistical significance	No signifi- cant differ- ence	Physical arousal was significantly greater than mental arousal	No significant difference				

TABLE 1

I

DISCUSSION

During this study, we assessed participants' subjective reports of sexual arousal in comparison with neural activity detected by means of spinal cord fMRI. There were no significant differences in levels of reported MSA or PSA during the AV stimulation paradigm. Functional MRI results obtained during AV stimulation revealed significant responses within the thoracolumbar cord. Because the subjects were not performing any physical stimulation or movement during this time and because conditions of increased sexual arousal were confirmed by self-report, these results provide further support for the theory that psychogenic sexual responses are controlled by the sympathetic nervous system. Previous research in able-bodied women and those with spinal cord injuries, has demonstrated activation of the sympathetic nervous system facilitates female sexual arousal (Lorenz, Harte, Hamilton, & Meston, 2012; Meston & Gorzalka, 1996a, 1996b; Sipski et al., 2001). Moreover, there is an effect of the degree of sympathetic stimulation in that low or very high levels of sympathetic nervous system stimulation result in decreased genital arousal whereas moderate levels of stimulation are associated with higher genital arousal (Lorenz et al., 2012). During the AV stimulation there were fMRI signal changes noted in several areas of the thoracic, lumbar and sacral cord. These findings are consistent with subjects' self-reports of PSA in this paradigm. Furthermore the sacral spinal cord responses are likely also associated with increased genital vasocongestion as a result of MSA as genital sexual arousal is reported to be controlled by the parasympathetic nervous system in animal models (Cai et al., 2008).

During the MAN condition, subjects' level of PSA was significantly greater than their level of MSA. In addition, PSA levels were significantly higher during the MAN compared with the AV condition. Functional MRI results revealed diminished activity in the area of the right ventral horn of the thoracolumbar spinal cord. The observed decreased activity in the lumbar region of the ventral horn may signify a decrease in neuronal inhibitory input from supraspinal regions. The nucleus paragigantocellularis in the brainstem is known to be involved in the inhibition of spinal sexual reflexes and sends direct neuronal projections to the ventral horn and interneurons in the lumbosacral spinal cord (Marson, List, & McKenna, 1992; Marson & McKenna, 1992), which, in turn, project to nuclei in the lumbosacral spinal cord, including the sacral parasympathetic nucleus (Nadelhaft & Booth, 1984). Thus, the attenuation in descending inhibitory input may account for the observed decrease in activity in the lumbosacral spinal cord in conjunction with subjects' reports of increased PSA.

Subjects' reported levels of MSA and PSA were significantly higher during the COM condition compared with AV or MAN conditions. However, there was no significant difference between subjects' reported levels of MSA versus PSA during the COM condition. In this final paradigm, fMRI results demonstrated increased activity in regions of the right intermediolateral cell column, ventral horn and dorsal horn in the thoracolumbar spinal cord. In addition, there was increased activity in the right sacral parasympathetic nucleus and ventral horn alongside decreased activity in the left ventral horn in the lumbosacral spinal cord. These results support the hypothesis of the reciprocal nature of physical and mental sexual arousal as a result of psychogenic or reflexogenic sexual stimulation in healthy, able-bodied women and are consistent with previous findings that indicate multiple neurologic inputs are involved in triggering genital sexual responses (Cai et al., 2008; Giuliano et al., 2010; McKenna, 1997; Sipski, 2001; Sipski, Alexander, & Rosen, 1999). Moreover, the increased activity observed in the ventral horn of the lumbosacral regions during the combined stimulation condition may be indicative of increased neuronal input to the pudendal

motorneurons immediately prior to the onset of orgasm in the female subjects. This finding is consistent both with the rhythmic motor contractions of pudendal innervated muscles that occur during orgasm and with published literature showing pharmacological stimulation of pudendal motorneurons triggers ejaculatory reflexes in male rats (Staudt et al., 2011).

During both the MAN and COM stimulation in the present study, increased activity was observed along the right side of the lumbar spinal cord between the L1–L4 spinal segments. Therefore, given its location, we suspect that this activity likely reflects increased lumbar spinothalamic cell activity, which has been previously been shown to coordinate autonomic responses, sensory inputs and motor outflow to trigger ejaculation in male rats (Allard et al., 2005; Coolen et al., 2004; Kozyrev, Lehman, & Coolen, 2012; Staudt et al., 2011; Truitt & Coolen, 2002). The lumbar spinothalamic cells are located in lumbar levels L3-L4 surrounding the central canal in lamina X and the medial portion of lamina VII, and are activated specifically with ejaculation in male rats. In addition, targeted lesions of the lumbar spinothalamic cells abolishes ejaculation but not other components of male rat sexual behavior (Coolen et al., 2004; Staudt et al., 2011; Truitt & Coolen, 2002; Truitt, Shipley, Veening, & Coolen, 2003). In this study, increased activity was observed in the vicinity of the lumbar spinothalamic cells during the manual stimulation and the combined stimulation conditions. These findings are in contrast to a previous study that reported an absence of lumbar spinothalamic cell activation, as visualized with Fos-immunoreactivity, following vaginocervical stimulation in female rats (Truitt et al., 2003). This dissonance may be associated with interspecies differences (i.e., humans in the present study vs. rats), the method of stimulation (i.e., clitoral stimulation in present study vs. vaginocervical stimulation), or the sensitivity/specificity of the quantitative measure (fMRI in the present study vs. Fos staining).¹ Evidence suggests that the clitoris forms from the same structures as the penis during embryonic development and that they are homologous organs (Baskin et al., 1999; O'Connell, Sanjeevan, & Hutson, 2005; Shih, Cold, & Yang, 2013). Furthermore, a recent study reported the presence of the spinal pattern generator involved in the control of ejaculatory pattern in the female rat. Specifically, mechanical stimulation of the urethra, vagina and clitoris triggered an ejaculatory motor pattern-as visualized from recordings of the urethralis muscle contractions in the female rat (Carro-Juarez & Rodriguez-Manzo, 2006)-similar to the motor pattern observed in male rats during contractions of the muscle of the bulbocavernosus (Carro-Juarez, Cruz, & Rodriguez-Manzo, 2003; Carro-Juarez & Rodriguez-Manzo, 2008; Coolen, Allard, Truitt, & McKenna, 2004; Kozyrev, Lehman, & Coolen, 2012; Staudt, de Oliveira, Lehman, McKenna, & Coolen, 2010; Staudt et al., 2011; Truitt & Coolen, 2002), a marker of the expulsion component of ejaculation in rats (Coolen et al., 2004) and men (Gerstenberg, Levin, & Wagner, 1990). Furthermore, in a pilot study, electrical stimulation at the L1-L2 vertebral level has been reported to elicit pleasurable genital and orgasm-like sensations in women with orgasmic dysfunction; and the orgasmic dysfunction returned upon removal of the electrical nerve stimulation (Meloy & Southern, 2006). In light of the previous studies, activity observed in the region of the lumbar spinothalamic cells during the MAN and COM stimulation paradigms suggests that a spinal pattern generator for ejaculation may exist in women and may be involved in the integration of autonomic outflow (as

¹Note that fMRI responses are thought to reflect changes in the mean synaptic input to a given area, as opposed to the spiking activity (output) of the neurons located there (Figley & Stroman, 2011; Logothetis et al., 2001), whereas c-Fos staining codes for a transcription factor that is thought to mediate long-term changes in neural functioning (Kovacs, 2008).

indicated by activity present in the intermediolateral cell column and sacral parasympathetic nucleus) with spinal activity associated with the culmination of sexual activity (indicated by activity in the dorsal horn in the lumbosacral spinal cord). Although it has been previously reported that lumbar spinothalamic cells are specifically activated with ejaculation and not other components of sexual behavior (Staudt et al., 2011; Truitt & Coolen, 2002; Truitt et al., 2003), we observed increased spinal fMRI activity in the vicinity of the lumbar spinothalamic cells before orgasm, as verbally reported by the female volunteers. This suggests that this region of the spinal cord may receive inputs from the clitoris and supraspinal regions during sexual activity and begin the process of integrating these inputs with autonomic outflow from the intermediolateral cell column and sacral parasympathetic nucleus before the onset and possibly as part of a trigger for ejaculation and/or orgasm.

This study is unique in a number of ways. The present study is the first to report activity in specific regions of the thoracolumbar and lumbosacral spinal cord during different components of sexual behavior in women. In addition, the present study used functional MRI to visualize activity in the spinal cord, which is believed to be related to *neuronal input* (Figley & Stroman, 2011; Logothetis et al., 2001), whereas previous studies reported *neuronal activation* visualized with C-Fos and C-Fos mRNA that are indirect markers of recent neuronal activity (Kovacs, 1998, 2008) and phosphorylation of extracellular signal-kinases that are involved in cell signaling pathways (Murphy, Smith, Chen, Fingar, & Blenis, 2002). Therefore, neuronal activation in specific regions of the spinal cord during sexual activity as visualized with C-Fos and pERK may not represent analogous regions of the spinal cord receiving neuronal inputs during sexual activity as visualized with functional MRI.

Taken together, our findings provide support for the involvement of the thoracolumbar and lumbosacral spinal cord in female sexual function and are consistent with findings in women with spinal cord injuries that demonstrate an intact sacral reflex arc is necessary to achieve orgasm (Sipski et al., 2001). The present results are also consistent with the finding of climactic-like pudendal motor neuron firing in response to pudendal sensory nerve stimulation (Cai et al., 2008). We hypothesize that the activation of pudendal motorneurons (detected as activity in the ventral horn in the present study) is related to the rhythmic muscular contractions during orgasm and the lumbar spinothalamic cells (corresponding to activity in the lumbar spinal cord to the right of the central canal) are evidence of heightened sympathetic activity at the moment orgasm is triggered; however the specific role of this neurologic activity during female spinal sexual reflexes at present remains inconclusive. The present report serves as the first piece of evidence to support the involvement of the lumbar spinothalamic cells and pudendal motorneurons in the regulation of genital responses leading up to orgasm in women.

The laterality of the observed fMRI responses raises the issue of the handedness of subjects and whether they preferentially stimulated different sides of the genitals. Unfortunately during this study, we did not record handedness; however, data show that approximately 10% of the general population is left-handed (Holder, 1997). In light of this, we hypothesize that subjects preferentially stimulated the right side of their genitals, which may have increased neural activity on this side. Moreover, neuroplastic changes from historic repetitive genital stimulation could have resulted in increased activity on the right side of their spinal cord. Further studies are warranted to determine whether this laterality of fMRI changes is reproducible. In addition, future studies are warranted to determine whether changes in fMRI signals in the thoracolumbar and lumbosacral spinal cord can be used to document neuroplasticity as the reason for efficacy of therapies such as clitoral vacuum suction (Schroder et al., 2005), which is purported to work by attempting to retrain sacral reflex responses.

The results of this study represent the first in vivo glimpse of human sexual responses in the intact female spinal cord by means of spinal fMRI. Specifically, we have identified the key regions involved in the central nervous system control of sexual arousal in women, which include the intermediolateral cell column, sacral parasympathetic nucleus, and the dorsal commissural nucleus. Although fMRI may not afford the spatial resolution to specify the involvement of specific nuclei, our results are consistent with regions shown to be involved in various aspects of sexual function in animal studies. The present study clearly demonstrates that spinal fMRI can be used to map human female sexual responses and holds promise to provide essential information for treatment planning and outcome monitoring for women with sexual dysfunction. Furthermore, use of sequential fMRI studies may be useful to elucidate neuroplasticity associated with various treatments (e.g., clitoral vacuum suction) for female sexual dysfunction.

FUNDING

Funding for this research was provided by the Craig Neilsen Foundation (Grant #2786).

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